

Aus dem C. und O. Vogt - Institut für Hirnforschung der
Universität Düsseldorf
Direktor: Prof. Dr. A. Hopf

**A MORPHOMETRIC STUDY
OF THE DOPAMINE - CONTAINING CELL GROUPS
IN THE MESENCEPHALON OF NORMALS,
PARKINSON PATIENTS AND SCHIZOPHRENICS**

Dissertation
zur Erlangung des Grades eines Doktors der Medizin
Der Medizinischen Fakultät der Universität Düsseldorf

vorgelegt von
**BERNHARD BOGERTS, JOHANNES HÄNTSCH
UND MICHAEL HERZER**

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" Gedruckt mit Genehmigung der Medizinischen Fakultät der Universität Düsseldorf.

Der Dekan
der Medizinischen Fakultät
der Universität Düsseldorf

gez.: Prof.Dr.Brüster

Referent
gez.: Prof.Dr.Hopf

Korreferent
gez.: Prof.Dr.Wechsler

ABSTRACT

A quantitative study of the melanin-containing dopaminergic neurons of the nigrostriatal system (A 9) and of the mesolimbic system (A 10) was carried out on Nissl-stained serial sections of 9 normal brains, 6 age-matched brains of schizophrenics, 5 brains of paralysis agitans, and 6 brains of postencephalitic parkinsonism.

By contrast with most laboratory animals the A 10 cell group is not well developed in the human brain.

Both in Parkinson's disease with a known hypoactivity of dopamine neurons and in schizophrenia with a postulated hyperfunction of these systems, pathological alterations of the dopamine cell groups can be observed. In paralysis agitans the nigrostriatal and the mesolimbic cell groups exhibit a significant loss of neurons, while the remaining mesolimbic cells appear to be in better condition. In the postencephalitic parkinsonism both systems have almost completely disappeared with a significant loss of nerve and glial cells.

In schizophrenia there is a significant decrease in the volume of the nigrostriatal area. Here the mean volume of the glial nuclei is reduced, whereas the mean volume of the nerve cells is diminished in the mesolimbic part.

Introduction

There are three dopaminergic systems in the mammalian midbrain: (1) the nigrostriatal pathway, arising from pigmented cell bodies in the pars compacta of the substantia nigra (SN) and projecting rostrally to the corpus striatum; (2) the mesolimbic pathway, arising from pigmented cell bodies in the area tegmentalis ventralis (ATV) and ascending to various limbic areas including the nucleus accumbens lying rostroventrally in the striatal complex (Fallon and Moore, 1978, Ungerstedt, 1971); (3) the mesocortical pathway whose cell bodies are also situated in the ATV and whose axons ascend to terminate in several cortical areas including the frontal, the cingulate and the piriform cortex (Bannon et al., 1981; Carter and Fibiger, 1977, Emson and Koop, 1978, Lindvall et al., 1978).

It is now generally accepted that many of the symptoms of Parkinson's disease are related to a degeneration of the nigrostriatal system (Hornykiewicz, 1977), whereas little is known of the mesolimbic and mesocortical system in this disease (Farley et al., 1977). In contrast to the numerous qualitative (Alvord, 1968, Arbuthnott, 1976, Hassler, 1937, Klaue, 1940) and some quantitative (Alvord et al., 1975, Pakkenberg and Brody, 1965, Togi et al., 1976) histopathological investigations of the nigrostriatal neurons in Parkinson's disease, we are not aware of any such studies of mesocortical and mesolimbic cell groups.

Clinical interest in the mesocortical and in the mesolimbic dopamine systems was aroused by the suggestion of Stevens (1979) that in schizophrenia their function is disturbed. The dopamine hypothesis of schizophrenia has dominated biochemical and pharmacological research on this disorder for more than a decade (Berger, 1981, Crow, 1978, Meltzer and Stahl, 1976). The hypothesis, that schizophrenic symptoms reflect a functional hyperactivity of these systems, is based on the evidence that neuroleptics reduce schizophrenic symptoms by decreasing brain dopamine activity. In addition, agents which enhance central dopamine activity, such as cocaine or amphetamine, can cause a syndrome that is indistinguishable from acute schizophrenia (Carlson, 1978, Crow and Gillbe, 1976, Richter, 1978).

The question of whether at least some forms of the schizophrenic condition have an underlying cerebral pathology remains unanswered. Today there is still surprisingly little information concerning neuropathological changes of dopaminergic systems in schizophrenia.

The purpose of this study is to perform a extensive morphometric investigation of nerve cells and glial cells of these mesencephalic cell groups in normals, in the idiopathic and postencephalitic form of Parkinson's disease and in schizophrenia.

Material

Complete frontal serial sections of human brains from the collection of the C. und O. Vogt-Institute of Brain Research, University of Düsseldorf, were studied.

The pars compacta of the SN was examined in 9 brains of normal adults (control group), 6 brains of schizophrenic patients, 5 brains of paralysis agitans and 6 brains of postencephalitic parkinsonism.

Because of the unfavourable section of brains in the midline it was impossible to evaluate the ATV in all brains. Therefore we evaluated some additional brains, so that the ATV was studied in 9 normal, 8 schizophrenic, 6 paralysis agitans and 5 postencephalitic brains.

The normal and schizophrenic brains were collected between the years 1928 und 1953 (tab. 1 and 2), that is before the introduction of neuroleptic drug treatment. Similary the cases of paralysis agitans date from between 1932 and 1937 (tab. 3), those of postencephalitic parkinsonism between 1931 and 1935 (tab. 4), thus before anticholinergic drugs and l-dopa were used.

For the control group (tab. 1) normal brains without any indication of neurological or psychiatric disease in history, clinical examination and autopsy findings were used. The most prominent psychiatric symptoms of the schizophrenic cases are shown in tab. 2. All parkinson patients had tremor at rest, rigidity and hypokinesia. It was difficult

to define the duration of disease exactly. Concerning the cases of schizophrenia and paralysis agitans (tab. 3) disease duration was defined as the time between first diagnosis and death. In cases of postencephalitic parkinsonism we took the time between encephalitis and death (tab. 4). These patients had contracted encephalitis lethargica Economo between 1917 and 1927, but first signs of postencephalitic parkinsonism appeared after an interval of up to ten years.

All brains were uniformly prepared according to the method described by Vogt (1940). They were fixed by immersion in formalin 4 %, embedded in paraffin, cut in 20 μ m sections and stained with cresyl violet.

Methods

The pars compacta of the SN was outlined on 12 to 17 frontal serial sections evenly distributed from the rostral to the caudal pole as formerly described by Bogerts (1981). The distance between these sections was 0.5 - 1 mm. For the reasons discussed below, we subdivided the SN into 2 parts, using the lateral corner of portine nuclei and the medial pole of the n. ruber as topographical marker points (fig. 2): a medial part (med) including the paranigral nucleus, assuming that this part has a more mesolimbic function, and a larger lateral part (lat) with a predominantly nigro-striatal projection.

Within the ATV a group of cells, called *n. niger suboculomotorius* (A 10 area), situated dorsal to the *n. interpeduncularis*, was evaluated (fig. 1 and 2). We only studied left cerebral hemispheres with the exception of one right hemisphere of paralysis agitans and one of postencephalitic parkinsonism.

In each section the following parameters have been determined for the lateral and the medial part of the *pars compacta*, separately:

- 1) Volumes by planimetry of the serial sections on photographic enlargements ($\times 12$). (The thickness of sections was determined by focussing on the upper and lower surfaces of the section at a magnification of 1250.) Because of the shrinkage of paraffin material due to the histological preparation the volume calculated from serial sections was corrected by an average shrinkage factor of 1.89. This factor was determined in 30 brains of the Vogt collection by Lange et al. (1976). The value corresponds roughly to that found by other authors (Stephan, 1960, Bottcher, 1975, Mauritzen Dam, 1979).
- 2) Numerical densities of nerve and glial cells (number of cells per unit volume of tissue); we evaluated the nerve cell density from 200 - 400 microscopic fields at a magnification of 312 and the glial cell density from 40 - 70 fields at a magnification of 781, giving rise to a standard error mean (SEM) of not more than 10 %. The number of nerve cells was overestimated, because

cell bodies were counted instead of nuclei. (Nuclei were encountered seldom, because they were often covered by melanin granules).

We corrected these values after a determination of the average diameter of cells according the formula of Haug (1976) by the factor 0,46 for the larger nigra cells and the factor 0,56 for the smaller cells of the ATV.

3) Absolute number of nerve glial cells (= numerical cell density x volume). This value is independant of shrinkage.

4) Volumetric nerve and glial cell densities (relative volume in % occupied by certain structures in a given tissue) by the so-called "Hit-point Method" (Haug, 1976) at a magnification of 1250 in 400 - 1000 counting grids, involving SEM of not more than 10%.

5) The average volume of nerve cell bodies, nerve and glial cell nuclei (= volumetric density x fresh volume / absolute number of cells).

Within the ATV only the absolute number of nerve cells was directly determined from 4 - 6 sections separated by a distance of 0,25 - 0,5 mm. It was impossible to determine the volumetric density of these medial cells because of the deformation induced by the midline cut.

To exclude an influence of duration of autolysis on the parameters studied, we correlated the time between death and fixation in formalin (2 - 96 h) with all significant

parameters of the groups studied. The coefficient of correlation varied between $-0,521$ and $+0,726$. All P-values were greater than $0,1$. Thus no correlation could be detected.

To test significant differences we used the Mann-Whitney-U-Test.

Results

1. Normal anatomy of the dopamine-containing cell groups in the human brain

a) Qualitative description

As yet the distribution of dopamine neuron systems in the adult human midbrain has not been mapped with fluorescence histochemical or immunohistological methods on account of the difficulties in the preparation of large brains with these techniques.

We have demonstrated in a previous paper that in the adult human brain neuromelanin is an excellent natural marker for all catecholaminergic cells in the lower brainstem, and that the dopamine-producing neurons in the mesencephalon are identical with melanin-containing cell groups within the pars compacta of the SN, the paranigral nucleus, the n. pedunculopontinus dissipatus, and the ATV (Bogerts, 1981).

The melanin-containing neurons form a continuous sheet of black pigmented cell bodies extending across the midline over the interpeduncular nucleus laterally out in the pars compacta of the SN (area A 9 according to Dahlström and Fuxe, 1964) on each side. The mid-line portion in the ATV is referred to as the A 10 area, while the caudal extension in the n. pedunculopontinus dissipatus, above and lateral to the SN is termed the A 8 area (fig. 1). The pars reticularis of the SN appears to lack melanin-containing cells.

Principally, the arrangement of the mesencephalic melanin cells is similar to the distribution of catecholamine producing cells in the rat brain. However, in the rat the largest dopamine cell group is the A 10 group of the ventromedial tegmentum (Dahlström and Fuxe, 1964); whereas, in the adult human brain the SN cell group predominates. The human A 10 group is rudimentary: only a small group of pigmented cell bodies is situated dorsally and laterally to the inter peduncular nucleus. In the old neuroanatomical literature this cell group is called "n. niger suboculomotorius" (Hassler, 1937) because of its ventral localisation to the n. oculomotorius (fig. 1 and 2).

It is important to note that most cells in the ATV and SN are dopamine neurons, there are numerous cells particularly in the ATV that do not contain melanin. The majority of cells situated exactly in the mid-line within the pars ventralis of the n. supratrochlearis (fig. 1) (= n. linearis) and most cells in the triangle between the interpeduncular nucleus, the niger suboculomotorius and the medial pole of the SN (fig. 1 and 2) do not contain melanin. In the monkey (Hubbert and Di Carlo, 1974) and in human fetuses (Nobin and Björklund, 1973) the n. linearis is reported to produce serotonin as transmitter (fig. 1 and 2). We did not evaluate these areas.

The A 8 area in the n. pedunculopontinus dissipatus in the formatio reticularis mesencephali extends without sharp

boundaries medioventrally through the medial lemniscus into the lateral parts of the SN and caudally into the rostral tegmentum of the pons. Very few melanin cells exist within this area. In each of our 20 μ m thick sections we saw not more than 3 - 6 pigmented neurons. We did not determine the total number of these cells, because of the lack of sharp boundaries of A 8.

b) Quantitative evaluation of A 9 and A 10 in normals
As shown in tab. 5 the mean total number of melanin cell bodies evaluated in 9 normal brains within the SN is about 300 000, whereas the estimated number of melanin cells in the n. suboculomotorius, which roughly corresponds to A 10, is only about 5 000. These data demonstrate that in the human A 9 there are about 60 times more melanin neurons than in A 10.

2. Quantitative evaluation of SN in Parkinson patients and schizophrenics

a) Paralysis agitans (tab. 6)

5 brains of paralysis agitans (72 ± 3 years)(mean $\pm$ SD) (tab. 3) were compared with 9 normal brains (43 ± 6 years). Because of the difference of age between the two groups we correlated the values of the normal group with the age (tab. 9). The coefficients of correlation varied between -0,199 and 0,370. The corresponding P-values all exceeded 0,1. Thus in our cases no significant decrease

in cell numbers and cell volumes dependant on age could be detected.

Fresh volume:

In the lateral part the fresh volume shrinks for about 28 % ($P = 0,01$) whereas there is very little change of volume in the medial part.

Nerve cells:

The absolute number of nerve cells is reduced by 66 % ($P < 0,001$) in the lateral part, in the medial part by 63 % ($P = 0,001$). The volume of nerve cell bodies is reduced by 39 % ($P < 0,05$) in the lateral part, but in the medial part only a trend in volume reduction (24 %; $P < 0,08$) can be seen. The nerve cell nuclei shrink by about 60 % ($P < 0,02$) in the lateral part, in the medial part there is no difference.

Glial cells:

With respect to the absolute number of glial cells no difference can be found in either the lateral or in the medial part. The volume of glial cell nuclei is unchanged.

b) Postencephalitic Parkinsonism (tab. 6)

6 brains of postencephalitic parkinsonism (54 ± 6 years) (tab. 4) were compared with 9 normal brains (43 ± 6 years).

Fresh volume:

The fresh volume is reduced by about 70 % ($P < 0,001$) in the lateral, by about 62 % ($P < 0,001$) in the medial part.

Nerve cells:

The absolute number of nerve cells is diminished by 94 % ($P < 0,001$) in the lateral, by 95 % ($P < 0,001$) in the medial part, that means there is a 20 fold reduction. The volume of nerve cell bodies is reduced by 52 % ($P < 0,005$) in the lateral part, the perikarya of the medial groups show a trend in the same direction.

Glial cells:

The absolute number of glial cells is diminished by 46 % ($P < 0,001$) in the lateral part, in the medial part by about 41 % ($P < 0,05$). Since there is a shrinkage of fresh volume by 70 % in the lateral and by 62 % in the medial part a relative gliosis has in fact been developing. No significant change concerning glial cell nuclei can be stated.

c) Schizophrenia (tab. 7)

6 schizophrenic brains (51 ± 7 years) were compared with 6 normal brains of similar age (48 ± 8 years).

Fresh volume:

There is a significant reduction of fresh volume in the lateral part of the SN of about 21 % ($P = 0,01$). The medial part is unaltered.

Nerve cells:

The absolute number of nerve cells has not changed in the medial and lateral part. While there is no definite reduction in volume of the nerve cell bodies in the lateral part, there is a significant reduction of about 16 %

($P < 0,005$) in the medial part. In neither the lateral nor in the medial division does the volume of nerve cell nuclei change significantly.

Glial cells:

No significant differences in absolute number of glial cells could be found. Thus, it can be stated that there is an increased density of glial cells because of the volume shrinkage in the lateral part. The volume of glial cell nuclei is significantly reduced by about 31 % ($P < 0,025$) in the lateral part. In the medial part there is a barely significant reduction of about 33 % ($P \approx 0,07$).

3. Nucleus niger suboculomotorius (A 10) in schizophrenics and Parkinson patients (tab. 8)

We compared 8 schizophrenic brains (47 ± 7 years), 6 brains of paralysis agitans (72 ± 7 years), 5 brains of postencephalitic parkinsonism (50 ± 6 years) with 9 normal brains (51 ± 8 years). The groups of schizophrenic and postencephalitic parkinsonian brains are nearly of the same age as those of the control group (tab. 1, 2 and 4). In the group of schizophrenic brains there is a reduction in the number of cells by about 16 % without reaching the level of significance. In A 10 of the paralysis agitans group an evident reduction of the number of cells by about 40 % can be stated ($P < 0,01$). The group of postencephalitic parkinsonism shows a reduction of number of nerve cells by nearly 97 % ($P < 0,001$). No

correlation between number of nerve cells and age could be found in the normal group (coefficient of correlation $r = -0,397$, $P\text{-value} > 0,1$).

A summary of tests of significance is given on Table 10.

Discussion

1. Normal anatomy

Although several authors (Hassler, 1937, Stern, 1936, Olszewski and Baxter, 1954) scrutinized the cytoarchitecture of the midbrain and substantia nigra, up to now no comparison of these cell groups has been made with the fluorescence- and immunohistological findings in laboratory animals (Di Carlo et al., 1973, Felten et al., 1974, Garver and Sladek, 1975, Hartman and Udenfried, 1970, Hökfelt et al., 1973, Jacobowitz and MacLean, 1978) or human fetuses (Nobin and Björklund, 1973, Olson et al., 1973).

In contrast to the rat, the human cell group A 10 is almost rudimentary. The human A 9 contains about 60 times more melanin neurons than A 10. Therefore one must be cautious in relating the results of experimental investigations in animals such as the rat, where this area is well developed, to humans, in particular to cases of schizophrenia (Fuxe et al., 1977, Iverson and Koop, 1977, Le Moal et al., 1977, Stevens, 1976).

However, some human limbic forebrain nuclei, for instance the n. accumbens and the olfactory tubercle, are reported to contain considerable concentrations of dopamine (Bird et al., 1978, Farley et al., 1977). Dopaminergic terminals have also been described in the human (Berger, 1977) and monkey (Brown et al., 1979) frontal cortex. It seems unlikely that in the human brain such a small cell group as the n. niger suboculomotorius corresponding to the original mesolimbic area A 10 is the sole source of

dopamine terminals in these large areas. Therefore, it is more than likely that in man, analogous to some laboratory animals, the medial parts of SN including the paranigral nucleus supply also limbic and neocortical structures with dopamine, and have a more mesolimbic and/or mesocortical than a nigrostriatal function.

An important difficulty in evaluating the mesolimbic and nigrostriatal neurons separately in the human is the lack of knowledge of which cell group innervates the limbic forebrain and the frontal cortex. The topography of the projection of these mesencephalic neurons on the basal forebrain, cortex and striatum has been analyzed using anterograde and retrograde tracing techniques in some laboratory animals (Fallon and Moore, 1978, Simon et al., 1979, Ungerstedt, 1971). From earlier studies (Ungerstedt, 1971), the nigrostriatal pathway has been thought to arise largely from the pars compacta of the SN, whereas mesolimbic and mesocortical dopamine systems were thought to arise only from the ATV. Later investigations did not support this strict parcellation of the dopamine cell groups and projection systems, but rather suggested that the dopamine cell groups form a continuum with both the ATV and the SN providing projections to the majority of the telencephalic terminal fields. Furthermore it was suggested that the projection of the 'ATV-SN system' is roughly topographically organized including an important medial-lateral component with the medial sectors of the ATV-SN area projecting

predominantly to the medial parts of nuclei in the basal forebrain, cortex and neostriatum, whereas the lateral sectors of the ATV-SN project more to the lateral parts of the neostriatum (Fallon and Moore, 1978). This separation is not exclusive since one cell may contribute fibers to both systems, for example some dopamine fibers were found to bifurcate with one branch innervating the neostriatum and the other innervating the adjacent amygdala (Fallon and Moore, 1978). In addition, fluorescent retrograde double labeling studies demonstrate that nigral and ATV neurons have divergent axon collaterals which interdigitate across the mediolateral extent (Kooy, 1979). For our evaluation we divided the pars compacta of the SN into a medial third assuming that there are more mesolimbic neurons and in two lateral thirds with more nigrostriatal function (fig. 2).

2. Paralysis agitans

There exists an abundant literature on qualitative descriptions of the neuropathological alterations in Parkinson's disease and there are excellent reviews (Alvord, 1968, Birkmayer and Riederer, 1980, Hornykiewicz, 1978, Rinne, 1978). Quantitative studies on the SN in Parkinson's disease are rather scarce. Pakkenberg and Brody (1965) counted the nerve cells in one section of 10 control and 10 paralysis agitans cases. They found a decrease of 66% of melanin containing nerve cells. Tolpanen (1971) performed neuron counts using a automatic image analyser. She found the same degree of cell loss. Tohgi et al. (1976) described a cell decrease

of 70 % in Parkinson cases with nigral depigmentation. Alford et al. (1975) graded the nerve cell loss on an arbitrary scale semiquantitatively; the mean estimated reduction was about 50 %. Bernheimer et al. (1973) determined the reduction of melanin cells also in a semiquantitative manner and correlated it with biochemical data. The degree of dopamine deficiency in the striatum was directly proportional to the degree of cell loss in the SN. Riederer and Wuketisch (1976) assumed a linear degeneration of nigrostriatal dopaminergic neurons, and concluded that Parkinson's disease begins 20 to 30 years before the appearance of the characteristic symptoms (akinesia, tremor and rigor). None of the above mentioned authors carried out subdivisions in medial and lateral parts and no volumetric measurements were performed.

We found in both, the medial more mesolimbic/mesocortical part and the lateral more extrapyramidal part of the SN, pars compacta a nerve cell loss of 60 to 70 %. In the n. niger suboculomotorius the cell loss (40 %) is not so severe. In this extremely heterogeneous area there are not only melanin containing dopaminergic neurons but also other very different cell types. In the monkey brain some of these are reported to be serotonergic (Hubbard and Di Carlo, 1974). May be these cells are less affected by the disease.

The volume of lateral SN shrinks. Interestingly, despite the loss of nerve cells no shrinkage of the medial part could be observed. Probably the numerous ascending and descending fibers of the medial forebrain bundle

traversing the medial SN division (Nauta, 1978) prevent a significant shrinkage.

In the nigrostriatal section the mean volume of the remaining perikarya is less reduced (30 %) than that of the nerve cell nuclei (60 %). Because of this considerable difference we assume in paralysis agitans a primary degeneration of the nuclei and a secondary atrophy or hypotrophy of the perikarya. In the medial part only a weak trend towards a reduction of the volumes of the perikarya and nuclei could be seen.

The present data reveal that mesolimbic and nigrostriatal parts of the mesencephalic melanin cell groups are affected to a different extent, and up to a point, support the results of Hassler's (1937) earlier qualitative description. This pointed out that degenerative changes in the medial cell groups are less severe. Although both parts lose 2/3 of their neurons, the volume of the remaining nerve cells of the medial groups seems to be better preserved.

The absolute number of glial cells has not changed. Observations that the number of glial cells increases in paralysis agitans (Greenfield, 1958), a change described as reactive gliosis, or glial scars, can not be confirmed. The increased glial cell densities encountered in sites with heavy loss of neurons are the result of the tissue shrinkage simulating an increased absolute number of glial cells.

There exists on study on dopamine in the limbic regions in Parkinson's disease (Farley et al., 1977). A marked decrease in dopamine levels was apparent in the parolfactory gyrus and the n. accumbens (62 %). These results fit with the degree of cell loss in the medial part. No major changes in dopamine content could be shown in the olfactory areas. These areas are probably innervated from the better preserved n. niger suboculomotorius.

The nerve cell loss in nigrostriatal and mesolimbic/mesocortical dopamine cell groups in paralysis agitans has some functional implications. The two systems are reported to have dissociable functions (Deniau et al., 1979, Bannon et al., 1981, Fuxe et al., 1977) the mesolimbic system mediating locomotion and mental activity, whereas the striatal system with its output to classic motor circuits is involved in the general modulation of motor organization and motor tone (Hassler, 1978, Iversen and Koop, 1977, Price et al., 1979); its degeneration probably causes rigidity and akinesia. The mesolimbic dopamine system may have a role in motivated behaviour, triggering activity in the striatal system (Iversen and Koop, 1977). Loss of its neurons could be responsible for other symptoms commonly seen in paralysis agitans such as starting inhibition, lack of initiative, slowness of thinking, and depression. Finally, it should be mentioned that the clinical symptomatology of this disease cannot be explained upon

the basis of pathology of the SN alone (Mettler, 1964). Degenerative changes have been described in other nuclei e.g. the noradrenergic locus coeruleus (Beheim-Schwarznach, 1954, Forné and Alvord, 1975), the cholinergic basal nucleus (Hassler, 1937), the cortex (Alvord et al., 1975) and even in the sympathetic ganglia (Rajput and Rozdilsky, 1977). Biochemical alterations of a lesser magnitude than that of dopamine are seen in other transmitter systems (serotonin, noradrenalin, cholinacetyltransferase, glutamyl acid decarboxylase) (Curzon, 1978, Gaspar et al., 1980, Mc Geer and Mc Geer, 1976, Loyd, 1978, Riederer et al., 1978).

3. Postencephalitic Parkinsonism

Postencephalitic Parkinsonism, developing as a sequel to lethargic encephalitis during first world war has probably been a transient phase in the epidemiology of Parkinson's disease and is now disappearing (Marttila and Rinne, 1979). In our cases all melanin cell groups have nearly completely disappeared. In the lateral and medial parts of the pars compacta of the SN about 5 % of the neurons are preserved, in the n. niger suboculomotorius less than 3 %. The shrunken volume of both parts (70 %) leads to increased glial densities seen in the tissue as glial scars. Nevertheless, the absolute number of glial cells is 40 - 50 % lower. The considerable loss of glial cells indicates that in postencephalitic parkinsonism the degenerative process affects both nerve

cells and glia. Earlier opinions that a reactive gliosis occurs with increasing numbers of glial cells have to be corrected in this disorder as well as in paralysis agitans.

By analogy with postencephalitic parkinsonism a reduction of the absolute number of glial cells was found by other authors in the degenerated striatum in Huntington's chorea (Lange et al., 1976). Therefore, one could discuss the possibility that chronic degenerative diseases, contrary to acute inflammatory and traumatic diseases (Greenfield, 1958), cause a degeneration of nerve cells and glial cells.

4. Schizophrenia

It is surprising that despite the numerous publications of the dopamine hypothesis of schizophrenia (Abramsky and Litvin, 1979, Berger, 1981, Crow, 1978, Meltzer and Stahl, 1976, Richter, 1978) no neuropathological investigations of the dopaminergic cell groups in the midbrain exist. Reviewing the literature back to 1900 we found only one qualitative study of the pars compacta of the SN (Nagasaka, 1925). The author could find no major changes except a pallor of the medial cell groups.

In our 6 age matched schizophrenic cases a significant reduction (20 %) of the volume of the lateral two thirds without cell loss or shrinkage of perikarya or nuclei could be detected. This implies that there has been a

reduction of the neuropil, consisting of afferent GABAergic, SPergic and enkephalinergic fibers from the striatum (Cooper et al., 1980, Cuello et al., 1981, Emson et al., 1980, Fonnum et al., 1978, Gramsch et al., 1979, Jessell et al., 1978, Staines et al., 1980), of afferent fibers from various cortical areas (Hassler et al., 1979) and glial cells. The protoplasm of the glial cells was not visible in the Nissl stained sections, but the volume of the glial nuclei is significantly diminished (30 %) in the nigrostriatal part and probably in the mesolimbic/mesocortical parts, too. The volume of the medial third is unaltered; here a shrinkage of perikarya (20 %) takes place.

The present data provide neither direct support for hypotheses that dopamine neurons are overactive in schizophrenia nor can they explain the finding of increased dopamine concentrations in the n. accumbens and anterior perforated substance (Bird et al., 1978), for it is unlikely that the hypotrophic cells in the medial part can supply these structures with more dopamine. Other studies failed to confirm increased dopamine concentrations or turnover in the limbic forebrain areas (Crow et al., 1979, Owen et al., 1978). On the other hand, a functional hyperactivity of the brain dopamine systems could be caused by supersensitivity of postsynaptic dopamine receptors (Arbuthnott, 1976, Lee et al., 1978, Owen et al., 1978). It is possible that the hypotrophy of the neurons of the mesolimbic

part causes a partial deafferentiation leading to a denervation hypersensitivity (Chouinard and Jones, 1978, Kapit, 1978) of the target structures which then react abnormally to increased dopamine production e.g. in stress situations (Woodrow and Reifmann, 1978).

Furthermore, it is possible that degenerated GABAergic terminals in the shrunken nigrostriatal part lead to a lack of inhibitory influence and thus to a increased activity of the postsynaptic dopamine neurons (Fuxe et al., 1977, Perry et al., 1979, Stevens, 1976).

The explanation of the decreased volume of glial nuclei is obscure. Miyakawa et al. (1972) described lipofuscin-like material in the cytoplasm of the oligodendroglia of schizophrenics. If the true functional unit of the brain ist not the neuron but rather the neuron-glial complex, then both neuronal and glial cells could be involved in mental diseases.

The complex symptomatology of "the group of schizophrenias" (Bleuler, 1911) cannot be explained by simple degeneration models of one cell group alone. Until now, qualitative descriptions of neuropathological alterations in the basal nucleus (Averback, 1981, Buttler-Brentano, 1952, Buttler-Brentano, 1956), the locus coeruleus (Beheim-Schwarzbach, 1954) the pallidum (Hopf, 1954) and the lower brainstem (Fishman, 1975) are not yet refuted, whereas reports of neuronal degenerations in the thalamus (Bäumer, 1954, Fünfgeld, 1925, Fünfgeld, 1952, Hempel, 1958, Vogt, 1948) have been challenged (Heyck, 1954, Peters, 1964).

A few quantitative studies of other areas exist: Dom et al. (1981) found a significant reduction in the density of interneurons in the pulvinar and smaller diameters of the interneurons in the caudate nucleus, the putamen and the n. accumbens. Hempel and Treff (1960) described lower cell densities in the medio-dorsal nucleus of thalamus, Colon (1972) lowered cell densities and reduced depth of some cortical areas. Recent studies of cerebral structures quantified from computerized tomography (CT) have indicated that many schizophrenic patients have enlarged ventricles indicating an atrophy of surrounding brain structures (Gattaz et al., 1981, Johnstone et al., 1976, Tanaka et al., 1981, Weinberger and Torrey, 1979). Therefore, we assume that the degenerative changes in the mesencephalic melanin systems in schizophrenics which are much less distinct than those found in Parkinson's disease are a part of a more generalized process affecting several brain areas.

Both in Parkinson's disease with a known hypoactivity of dopamine neurons and in schizophrenia with a postulated hyperfunction of these systems, pathological alterations of the dopamine cell groups can be observed. In Parkinson's disease mainly the nerve cells are degenerated, whereas in schizophrenia these cells seem to be well preserved (except that they show a slight hypotrophy). In the latter disease the neuropil and the glial nuclei are affected.

brain	age	sex	cause of death	studied structures	
				S N	A 10
A 58	24	m	haemorrhagic shock	+	+
A 65	40	f	veronalism (suicide)	+	+
A 70	36	f	veronalism (suicide)	+	+
A 88	62	m	peritonitis, carcinoma of the stomach	+	-
A 61	38	m	coma uraemicum	+	+
A 97	39	m	pulmonary embolism	+	+
A 85	30	f	fat embolism after a street accident	+	-
A 77	37	m	decapitation (1943)	+	+
A 64	84	m	pneumonia	+	+
A 76	100	f	death by senile decay	-	+
A 56	56	m	laryngeal cancer death under the operation	-	+

Table 1 : Control brains without neurological or psychiatric diseases
(+ = evaluated, - = not evaluated)

brain	age	sex	year of death cause of death	most prominent psychiatric symptoms	time between diagnosis and death	studied SN	areas A 10
M 5	53	f	1953, bronchopn.	haptic, auditory, gustatory hallucinations, delusion of being harmed, persecution complex	1 month	+	-
Hö 5	36	m	1951, circulatory breakdown an electric shock	incoherency of thinking, coenaesthetic and paranoid symptoms, auditory hallucina- tions, catatonic stupor, mutism.	12 years	+	+
Bu 62	64	f	1933, dropped out of a window	auditory hallucinations, per- secution complex	24 years	+	+
Bu 54	38	f	1933, bronchopn.	catatonic behaviour, manierism, feeling to be burnt	16 days	+	+
Bu 8	78	m	1930, peritonitis	persecution complex, auditory hallucinations, paranoid ideas	3 years	+	+
Bu 1	37	f	1928, sepsis	auditory hallucinations, delusion of culpability, catatonid	unknown	+	+
Bu 20	26	f	1930, bronchopn.	cataplexy, catatonid, mutism	7 years	-	+
Bu 52	24	m	1933, bronchopn.	stupor, stereotypy in posture and movement, catatonid, cataplexy	3 years	-	+
Bu 36	71	f	1931, sepsis, bronchopn.	father, mother, and one brother suffered from mental disorder; hieromani, toxicomania, phoneme	37 years	-	+

Table 2 : Schizophrenic cases (+ = evaluated, - = not evaluated)

brain	age	sex	year of death cause of death	most prominent psychiatric symptoms	time between diagnosis and death	studied SN	areas A 10
M 5	53	f	1953, bronchopn.	taptic, auditory, gustatory hallucinations, delusion of being harmed, persecution complex	1 month	+	-
Hö 5	36	m	1951, circulatory breakdown an electric shock	incoherency of thinking, coenaesthetic and paranoid symptoms, auditory hallucina- tions, catatonic stupor, mutism.	12 years	+	+
Bu 62	64	f	1933, dropped out of a window	auditory hallucinations, per- secution complex	24 years	+	+
Bu 54	38	f	1933, bronchopn.	catatonic behaviour, manierism, feeling to be burnt	16 days	+	+
Bu 8	78	m	1930, peritonitis	persecution complex, auditory hallucinations, paranoid ideas	3 years	+	+
Bu 1	37	f	1928, sepsis	auditory hallucinations, delusion of culpability, catatonia	unknown	+	+
Bu 20	26	f	1930, bronchopn.	cataplexy, catatonia, mutism	7 years	-	+
Bu 52	24	m	1933, bronchopn.	stupor, stereotypy in posture and movement, catatonia, cataplexy	3 years	-	+
Bu 36	71	f	1931, sepsis, bronchopn.	father, mother, and one brother suffered from mental disorder; bieromania, toxicomania, phoneme	37 years	-	+

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brain	age	sex	cause of death	studied structures	
				S N	A 10
A 58	24	m	haemorrhagic shock	+	+
A 65	40	f	veronalism (suicide)	+	+
A 70	56	f	veronalism (suicide)	+	+
A 88	62	m	peritonitis, carcinoma of the stomach	+	-
A 61	38	m	coma uraemicum	+	+
A 97	39	m	pulmonary embolism	+	+
A 85	30	f	fat embolism after a street accident	+	-
A 77	37	m	decapitation (1943)	+	+
A 64	84	m	pneumonia	+	+
A 76	100	f	death by senile decay	-	+
A 56	56	m	laryngeal cancer death under the operation	-	+

Table 1 : Control brains without neurological or psychiatric diseases
(+ = evaluated, - = not evaluated)

brain	age	sex	year of death cause of death	time between first diagnosis and death	studied SN	structures A 10
C 51	79	m	1936, bronchopn.	unknown	+	+
Bu 56	71	f	1933, bronchopn.	4 years	+	+
Bu 99	68	m	1937, bronchopn.	8 years	+	-
Bu 69	78	m	1934, bronchopn.	unknown	+	+
Bu 47	67	m	1932, bronchopn.	11 years	+	+
Rö 66	66	m	1934, bronchopn.	6 years	-	+
C 13	70	m	1933, myocardial infarction	7 years	-	+

Table 3 : Paralysis agitans; all patients had tremor at rest, rigidity, and hypokinesia
(+ = evaluated, - = not evaluated)

brain	age	sex	year of death cause of death	time between encephalitis and death	studied SN	structures A 10
Bu 85	68	m	1935, aspiration pneumonia	14 years	+	-
C 22	52	m	1934, bronchopn.	12 years	+	+
Bu 73	32	f	1934, pneumonia	11 years	+	+
Bu 39	46	m	1931, bronchopn.	11 years	+	+
Bu 71	63	m	1934, bronchopn.	8 years	+	+
Bu 64	59	m	1933, myocardial infarction	11 years	+	+

Table 4 : Postencephalitic parkinsonism; all patients had tremor at rest, rigidity, and hypokinesia

SN, p.comp.	292000	±	20000	(9)
A 10 (n. niger suboculomotorius)	5100	±	530	(9)

Table 5 : Absolute number of melanin containing nerve cells within the pars compacta of the substantia nigra (SN, p. comp.) and the n. niger suboculomotorius (A 10); values expressed as mean ± SEM, number of brains in parenthesis

NORMAL BRAINS

PARALYSIS AGITANS BRAINS

POSTENCEPHALITIC BRAINS

fresh volume in mm ³	lat	204 ±	14 (9)	146 ±	14 (5)	**	62 ±	7 (6)	***
	med	64 ±	6 (9)	57 ±	5 (5)	ns	24 ±	5 (6)	***
absolute number of nerve cells	lat	200212 ±	11034 (9)	68307 ±	5940 (5)	***	11256 ±	2681 (6)	***
	med	90829 ±	9314 (9)	33407 ±	6498 (5)	***	4328 ±	1651 (6)	***
absolute number of glial cells (10 ³)	lat	9119 ±	629 (9)	8122 ±	1119 (5)	ns	4953 ±	16 (6)	***
	med	2667 ±	272 (9)	3194 ±	467 (5)	ns	1881 ±	294 (6)	*
volume of the nerve cell bodies in μm ³	lat	16321 ±	1438 (7)	9988 ±	2541 (5)	+	7903 ±	1436 (6)	**
	med	14172 ±	702 (7)	10766 ±	2363 (5)	ns	8958 ±	2060 (6)	ns
volume of the nerve cell nuclei in μm ³	lat	1617 ±	304 (7)	645 ±	95 (5)	*	981 ±	143 (6)	ns
	med	1746 ±	274 (7)	1455 ±	365 (5)	ns	1319 ±	464 (6)	ns
volume of the glial cell nuclei in μm ³	lat	92 ±	18 (7)	73 ±	6 (5)	ns	62 ±	12 (6)	ns
	med	88 ±	15 (7)	71 ±	6 (5)	ns	62 ±	11 (6)	ns

Table 6 : Results of the quantitative evaluation of the parkinsonian brains; lat = lateral part of the SN, p. comp./med = medial part of the SN, p. comp.; values expressed as mean ± SEM, number of samples in parenthesis; + = P<0.05, ** = P<0.01, *** = P<0.001, ns = not significant, when compared with control values, using Mann-Whitney-U-test

fresh volume	lat med	208 + 69 +	13 (6) 7 (6)	165 + 61 +	6 (6) 4 (6)	** ns
absolute number of nerve cells	lat med	194282 + 93460 +	15422 (6) 12903 (6)	171596 + 89948 +	33825 (6) 7899 (6)	ns ns
absolute number of glial cells (10 ³)	lat med	9239 + 2862 +	91 (6) 364 (6)	8047 + 2759 +	409 (6) 177 (6)	ns ns
volume of the nerve cell bodies in μm^3	lat med	15255 + 13547 +	1141 (6) 380 (6)	12915 + 11334 +	678 (6) 97 (6)	ns **
volume of the nerve cell nuclei in μm^3	lat med	1281 + 1598 +	272 (6) 270 (6)	1315 + 1321 +	115 (6) 107 (6)	ns ns
volume of the glial cell nuclei in μm^3	lat glial cell nuclei	75 + 79 +	7 (6) 13 (6)	52 + 53 +	6 (6) 8 (6)	* ns (p=0.07)

Table 7 : Results of the quantitative evaluation of the schizophrenic cases; lat = lateral part of the SN, p. comp. med = medial part of the SN, p. comp.; values expressed as mean + SEM, number of samples in parenthesis; * = P<0.05, ** = P<0.01, *** = P<0.001, ns = not significant, when compare with control values, using Mann-Whitney-U-test

NORMALS	5155 ± 531	(9)	
PARALYSIS AGIT.	3100 ± 277	(6)	**
POSTENCEPHALITICS	133 ± 53	(5)	***
SCHIZOPHRENICS	4306 ± 332	(8)	ns

Table 8 : Absolute number of melanin containing nerve cells in the n. niger suboculomotorius (A 10) of all groups; values expressed as mean ± SEM, number of samples in parenthesis; * = $P < 0.01$, *** = $P < 0.001$, ns = not significant, when compared with the normal group, using Mann-Whitney-U-test

		corr. coeff.	f - stat	p - value
fresh volume	lat	- 0,058	0,024	$p > 0,1$
number of	lat	- 0,199	0,289	$p > 0,1$
nerve cells	med	0,074	0,038	$p > 0,1$
nerve cell bodies	lat	- 0,024	0,003	$p > 0,1$
nerve cell nuclei	med	0,370	0,793	$p > 0,1$

Table 9 : Dependence of the parameters with significant differences in the paralysis agitans cases on age, the only group not age matched; all p-values are greater than 0.1, thus in our cases no correlation could be detected

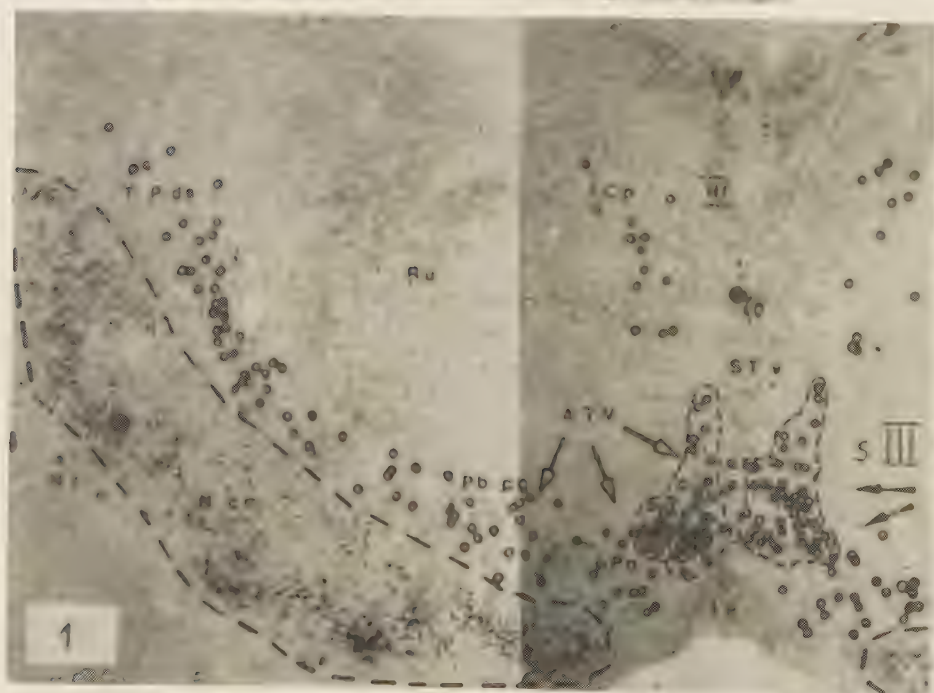
	NIGRO-STRIATAL		MESOLIMBIC-MESOCORTICAL			
	SUBSTANTIA NIGRA LAT.		SUBSTANTIA NIGRA MED.		N. NIGER SUBOCULOMOT.	
	SCHIZO- PHRENIA	PARAL. AGIT.	POST- ENC.P.	SCHIZO- PHRENIA	PARAL. AGIT.	POST- ENC.P.
volume	-21*	-28**	-70***	-11 ns	-62***	not evaluated
<u>NERVE CELLS</u>						
absolute number	-12 ns	-66***	-94***	-4 ns	-63**	-16 ns -40** -97***
volume perikarya	-15 ns	-39*	-52**	-16**	-24 ns	not evaluated
volume nuclei	+ 3 ns	-60*	-39 ns	-17 ns	-24 ns	not evaluated
<u>GLIAL CELLS</u>						
absolute number	-13 ns	-11 ns	-46***	-4 ns	-16 ns	not evaluated
volume nuclei	-31*	-21 ns	-32 ns	-33(+)	-19 ns -29 ns	not evaluated

Table 10 : Summary of the results showing the mean difference between normal and pathological cases in % and the degree of significance. * = P 0.05, ** = P 0.01, *** = P < 0.001, ns = not significant, when compared with control values, using Mann-Whitney-U-test.

Explanation to the figures

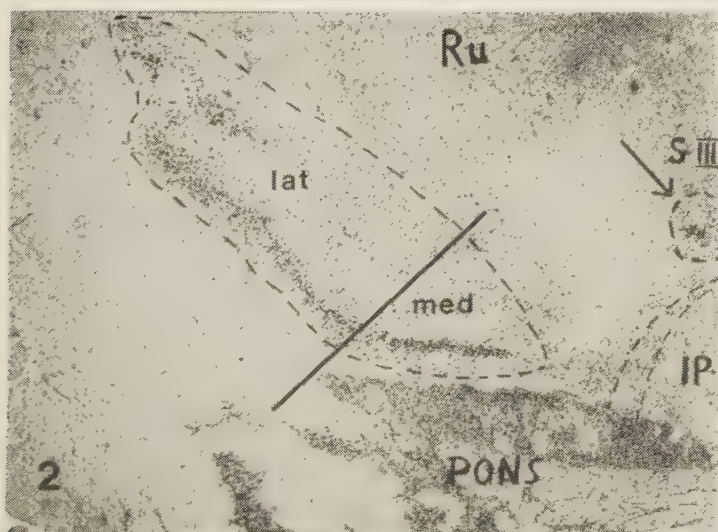
Fig. 1 Distribution of the dopaminergic cell groups in the midbrain of a 60 year old man, using melanin as a natural marker (Nissl stained frontal section at a magnification of x10; the adjacent myelin stained section has a x2.5 fold magnification).

Fig. 2 Frontal Nissl stained section at a magnification of 8 x. The pars compacta of the substantia nigra was divided in a medial third (med) including the paranigral nucleus assuming that this part has a more mesolimbic function, and in two lateral thirds (lat) with a more nigrostriatal projection, using the lateral corner of the pontine nuclei and the medial pole of the nucleus ruber as topographical marker points. The small cell group, marked with an arrow, dorsal to the interpeduncular nucleus corresponds to the mesolimbic/mesocortical nucleus niger suboculomotorius.



Abbreviations

ATV,	area tegmenti ventralis of Tsai (A 10)
EW,	n. Edinger-Westphal
Icp,	n. intracapsularis
Ncm,	n. niger compactus (A 9)
Nr,	n. niger reticularis
Ru,	n. ruber
STv,	n. supratrochlearis ventralis (= n. linearis)
S III,	n. niger suboculomotorius
III,	n. oculomotorius



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ACKNOWLEDGEMENTS

The authors wish to thank: Prof. Dr. A. Hopf (University of Düsseldorf), who supported all phases of this study; Dr. J.A. Büttner-Enever, Prof. G. Novotny, Prof. Dr. J.P. Huston (University of Düsseldorf), and Prof. Dr. T.J. Crow (Northwick Park Hospital, Middlesex, England) for their valuable comments on an earlier draft of this paper.

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